Guideline

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Recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 13–15 November 2016

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Abstract

About the meeting: The purpose of the European Stroke Organisation (ESO)-Karolinska Stroke Update Conference is to provide updates on recent stroke therapy research and to give an opportunity for the participants to discuss how these results may be implemented into clinical routine. Several scientific sessions discussed in the meeting and each session produced consensus statements. The meeting started 20 years ago as Karolinska Stroke Update, but since 2014, it is a joint conference with ESO. Importantly, it provides a platform for discussion on the ESO guidelines process and on recommendations to the ESO guidelines committee on specific topics. By this, it adds a direct influence from stroke professionals otherwise not involved in committees and work groups on the guidelines procedure. The discussions at the conference may also inspire new guidelines when motivated. The topics raised at the meeting are selected by the scientific programme committee mainly based on recent important scientific publications. The ESO-Karolinska Stroke Update consensus statement and recommendations will be published every 2 years and it will work as implementation of ESO-guidelines

Background: This year's ESO-Karolinska Stroke Update Meeting was held in Stockholm on 13–15 November 2016. There were 10 scientific sessions discussed in the meeting and each session produced a consensus statement (*Full version with background, issues, conclusions and references are published as web-material and at http://www.eso-karolinska.org/2016 and http://eso-stroke.org*) and recommendations which were prepared by a writing committee consisting of session chair(s), secretary and speakers and presented to the 312 participants of the meeting. In the open meeting, general participants commented on the consensus statement and recommendations and the final document were adjusted based on the discussion from the general participants.

Recommendations (grade of evidence) were graded according to the 1998 Karolinska Stroke Update meeting with regard to the strength of evidence. **Grade A Evidence:** Strong support from randomised controlled trials and statistical reviews (at least one randomised controlled trial plus one statistical review). **Grade B Evidence:** Support from randomised controlled trials and statistical reviews (one randomised controlled trial or one statistical review). **Grade C Evidence:** No reasonable support from randomised controlled trials, recommendations based on small randomised and/or non-randomised controlled trials evidence.

Keywords

Stroke, guideline, recommendation, consensus, cerebral infarct, intracerebral haemorrhage

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Session 1: Management of cervical artery dissection (CAD)

Chair: T. Tatlisumak (Gothenburg), Secretary: E. Lundström (Stockholm), Speakers: S. Debette (Bordeaux); H. Markus (Cambridge), Contributors: S. T. Engelter (Basel), M. Arnold (Bern)

1. What is the best method to diagnose CAD?

Contrast enhanced magnetic resonance imaging (MRI) angiography (MRA) and MRI with T1-fat suppression sequences is the recommended imaging modality to diagnose extra- and intracranial CAD. When not available computed tomography (CT) and CT angiography (CTA) might be alternatives grade C.

2. Acute stroke in the setting of CAD: Is thrombolysis safe?

Acute ischaemic stroke (AIS) patients with suspected or confirmed extracranial CAD should not be excluded from intravenous or intra-arterial thrombolysis or mechanical thrombectomy (grade C).

3. Should we use anticoagulants or antiplatelet drugs to prevent CAD?

For extracranial CAD:

a. Antithrombotic treatment is strongly recommended (Grade C).
b. There is no evidence of any difference between antiplatelets and anticoagulants (heparin followed by warfarin) (Grade B).

For intracranial dissection in the absence of SAH, antiplatelet drugs are recommended (Grade C).

4. Is there a role for angioplasty and stenting?

Angioplasty and stenting may be considered in CAD patients with recurrent ischaemic symptoms despite antithrombotic treatment (Grade C).

5. What is the optimal duration of medical treatment?

Antithrombotic treatment is recommended for at least 6–12 months. In patients in whom full recanalisation of the dissected artery has occurred and there have been no recurrent symptoms stopping antithrombotic treatment may be considered. In case of a residual dissecting aneurysm or stenosis, long-term antiplatelet treatment is recommended (Grade C).

Session 2: Update on secondary treatment in AIS

Chairs: N. Bornstein, Tel-Aviv, N. Ahmed, Stockholm, Secretary: C. Cooray, Stockholm, Speakers: M. Paciaroni/V. Caso, Perugia, R. Bulbulia (Oxford), H. Mattle (Bern), N. Bornstein (Tel Aviv)

Patients with atrial fibrillation and AIS-timing of anticoagulation

1. When is the best time for initiating anticoagulation treatment after AIS based on RAF study?

In patients with AIS and atrial fibrillation, we recommend that oral anticoagulation treatment may be started at day 4 in mild stroke and small infarct, at day 7 in moderate stroke with medium infarcts, and at day 14 in severe stroke with large infarcts from index stroke. More data from randomised controlled trials (RCTs) and prospective registries are needed to verify these time-points, in particular for direct oral anticoagulants (Grade C).

2. Should low molecular weight heparin (LMWH) not be used alone or prior to start of oral anticoagulation treatment in patients with AF and ischaemic stroke?

Based on observational study results, bridging therapy with LMWH, prior to oral anticoagulation therapy may not be used in patients with atrial fibrillation and ischaemic stroke (Grade C).

Prevention of stroke in patients with patent foramen ovale (PFO): An update

1. Are there sufficient data from the available RCTs to recommend device closure of a symptomatic (Stroke/TIA) PFO? To whom?

We recommend that percutaneous PFO closure should be offered to patients with cryptogenic stroke and a PFO provided that the PFO is likely stroke-related according to the RoPE score (Grade A).

2. Considering the best medical treatment-antiplatelets vs. anticoagulation. Long-term follow-up with no crossover and loss of follow-up in the studies is a serious concern. Are further studies feasible?

Current evidence did not show any difference in outcome comparing oral anticoagulation and antiplatelet

therapy for secondary stroke prevention in patients with PFO. We recommend future randomized trials comparing different antithrombotic/anticoagulant approaches in patients with cryptogenic stroke and PFO, especially trials that include the non-vitamin K antagonist (VKA) oral anticoagulants (Grade B).

3. Is the RoPE score good enough to differentiate between 'incidental' and 'causal' PFO?

Currently, the Risk of Paradoxical Embolism (RoPE) score represents the best tool to estimate the probability whether a discovered PFO is likely stroke-related or incidental. It is desirable that the ROPE score be validated in a prospective large cohort (Grade B).

Update on carotid surgery and stenting

1. Given the recent improvements in medical therapy, should we continue to base our treatment decisions on data from 'old' symptomatic carotid trials?

Patients with symptomatic carotid stenosis and a high risk of recurrent stroke (e.g. >70% carotid stenosis, ischaemic event <2 weeks previously) should be offered timely intervention with carotid intervention (Grade A).

Patients with symptomatic carotid stenosis and lower-risk of recurrent stroke (e.g. moderate carotid stenosis, retinal symptoms only, event > 2 weeks previously) may be randomised to trials comparing carotid intervention plus medical therapy vs. medical therapy alone (ECST-2/CREST-2) if clinician and patient substantially uncertain about the benefits of intervention (Grade B).

2. Is it ever appropriate to intervene on a <50% symptomatic stenosis?

Almost all patients with <50% symptomatic carotid stenosis should not be treated with intervention. However, intervention in certain patients may be considered if the stenosis causes recurrent symptoms despite optimal medical therapy (Grade C).

3. Does gender matter – Do women really derive less benefit from carotid intervention than men?

Decisions on whether or not to intervene on patients with carotid stenosis should not be based on gender (Grade A).

4. With more experience, better case selection and technological advances, can CAS compete with carotid endarterectomy?

Carotid artery stenting (CAS) is an effective alternative intervention in selected cases (e.g. not recently symptomatic, age <70 years, no prior ischaemic brain damage) when done by experienced interventionists. Technological advances in cerebral protection, access and stent design should be considered in patients treated with CAS (Grade A).

Session 3: Lipid lowering for primary and secondary stroke prevention – New guideline?

Chair: E. Berge (Oslo), Secretary: T. Prazeres Moreira (Stockholm), Speakers: G. Ntaios (Larissa) and A. Charidimou (London)

1. Should aggressive lipid lowering therapy be given for secondary prevention of stroke?

We recommend that statins be used as a part of standard secondary prophylactic treatment after an ischaemic stroke or a transient ischaemic attack (TIA). Benefits were observed both with atorvastatin 80 mg and with simvastatin 40 mg (Grade A). The use of statins in secondary prevention of ischaemic stroke caused by less frequent non-atherosclerotic etiologies such as arterial dissection and PFO requires further investigations.

2. Should lipid lowering therapy be given in the acute phase of stroke?

There is no evidence from RCTs to support the routine use of statins in the acute phase of stroke (first 2 weeks). However, observational studies do not show an increase in symptomatic ICH in patients previously treated with statins or to whom statin was given within 3 days after stroke. Statin treatment is thus recommended to start before discharge from hospital after an AIS or at least during follow-up (Grade C).

3. Should statins be used after intracerebral haemorrhage (ICH)?

Statins should be used with caution in patients with previous spontaneous ICH (Grade C) – changed from previous KSU recommendation. Avoiding high-dose statin regimens in patients with ICH should be considered (Grade A) – new. In a subgroup of patients with cerebral amyloid angiopathy-related lobar ICH, statin use should probably be reserved for compelling indications (Grade C).

4. Is there a place for PCSK9 inhibitors for patients with dyslipidaemia and previous stroke or transient ischaemic attack?

Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors could be considered for patients with previous ischaemic stroke or TIA who (a) have elevated LDL-cholesterol despite aggressive lipid-lowering treatment (defined as atorvastatin 40/80 mg (or rosuvastatin 20/40 mg) plus ezetimibe 10 mg), or (b) have specific statin-related complications (e.g. myopathy, rhabdomyolysis, other idiosyncratic side-effects) (Grade B).

5. Should lipid lowering therapy be given for primary prevention?

Lipid lowering treatment in combination with lifestyle changes is recommended for primary prevention in patients who have high 10-year risk for cardiovascular events (Grade A). The drug-class and the intensity of the lipid-lowering treatment as well as the treatment goals are thus depend on patient characteristics (Grade A).

Session 4: Guideline for prophylaxis for venous thromboembolism (VTE) (deep vein thrombosis (DVT)) in immobile patients with AIS

Chair: G.A Ford (Oxford), Secretary: M. Lantz (Stockholm), Speakers: V. Caso (Perugia), C. Sjöstrand (Stockholm)

A. To endorse the proposed guideline on prophylaxis for VTE in immobile patients with AIS as follows:
   1. We recommend that graduated compression stockings should not be used in patients with ischaemic stroke (Grade A).
   2. We recommend that intermittent pneumatic compression (IPC, thigh-length, sequential) should be used for immobile patients with ischaemic stroke. It should not be used in patients with open wounds on the legs and should be used with caution in those with existing DVT, heart failure, severe peripheral vascular disease or confusion (Grade A).
   3. To consider prophylactic anticoagulation with unfractionated heparin (UFH), LMWH or heparinoid in immobile patients with ischaemic stroke in whom the benefits of reducing the risk of VTE is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use (Grade A).
   4. Where prophylactic anticoagulation is indicated LMWH or heparinoid should be considered instead of UFH because of its greater reduction in risk of DVT, the greater convenience, reduced staff costs and patient comfort. These advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs and risks in elderly patients with poor renal function (Grade A).

B. To ask the ESO to consider the following remarks in relation to the new guidelines:
   1. IPC should be used for 30 days or until the patient is mobilizing independently.
   2. IPC should not be commenced if more than 72 h post stroke, unless pre-existing DVT has been ruled out.
   3. Prophylactic anticoagulation should be used if IPC is not tolerated. Treatment should be used for 30 days or until mobilized. Prophylactic anticoagulation may be used in combination with IPC in patients with high risk of VTE (e.g. active cancer, coagulation disorder or previous DVT).
   4. If prophylactic anticoagulation with LMWH is used, standard prophylaxis doses should be applied. For Enoxaprin subcutaneous injection of 40 mg once daily (20 mg if creatinine clearance <30 ml/min) and for Dalteparin subcutaneous injection of 5000 IE once daily (2500 IE if creatinine clearance <30 ml/min).
   5. The risk for bleeding should be assessed before VTE prophylaxis is administered. Research is needed to validate a risk assessment tool to evaluate bleeding risk in patients with ischaemic stroke.
   6. In patients with poor renal function (creatinine clearance <30 ml/min), or at higher risk for extracranial bleeding (e.g. recent GI bleeding, known gastric ulceration), UFH can be considered before LMWH.
   7. In other clinical settings, non-vitamin K oral antagonists (NOACs) have been shown to be effective for prophylactic treatment of VTE prophylaxis. Further research is warranted to investigate if NOAC may be an option for prophylaxis of VTE in patients with ischaemic stroke.

Session 5: Stroke, seizures and epilepsy

Chair: H. Christensen (Copenhagen), Secretary: A. Steinberg (Stockholm), Speakers: T. Tomson (Stockholm), M. Holtkamp (Berlin)

1. Should primary prophylaxis of acute symptomatic or unprovoked seizures be recommended after stroke?
   a. RCTs are few and underpowered, and the quality of evidence is generally low. As the risk of acute symptomatic and unprovoked seizures in stroke is low, we do not suggest general use of

anti-epileptic drugs (AEDs) in primary prevention after stroke. If treatment is initiated for primary prevention of acute symptomatic seizures, it should be withdrawn after the acute post-stroke phase. Although the risk of unprovoked seizures is considerably higher in patients with large ICH and cortical involvement as well as sinus VTE, primary prevention is rarely justified (Grade C).

b. RCTs are needed to assess the benefits of short- and long-term prophylaxis with AEDs for prevention of acute symptomatic and unprovoked seizures.

2. Should secondary prophylaxis of seizures be recommended after one or more acute symptomatic or unprovoked seizure in patients after stroke?
   a. RCTs are absent and quality of evidence generally low. Acute symptomatic seizures have a low risk of recurrence and thus short- and long-term prevention is not suggested. If treatment is initiated for secondary prevention of acute symptomatic seizures, it should be withdrawn after the acute post-stroke phase. Unprovoked seizures carry a high risk of recurrence and based on observational data, long-term AED should be considered. There are no conclusive RCT data specific to post-stroke populations to guide the choice of AEDs (Grade C evidence).
   b. RCTs are needed, both to assess potential benefit in reduction in risk of seizure recurrence and its consequences, but also in tolerability and adverse effects in this patient population.

Session 6: Management of acute stroke (ischaemic or haemorrhagic) under oral anticoagulant therapy

Chairs: C. Cordonnier (Lille) and K.R. Lees (Glasgow), Secretary: E. Eriksson (Stockholm), Speakers: B. Norrving (Lund), T. Steiner (Frankfurt/Heidelberg) R. Veltkamp (London).

Issue 1. How should we approach neurological emergencies when patients are on OACs?

1. In AIS, laboratory testing before intravenous thrombolysis (IVT) is necessary if relevant anticoagulant activity cannot be ruled out by medical history (Grade C).
2. In acute ICH, reversal of anticoagulation should be started as soon as possible after diagnosis of ICH unless relevant anticoagulant activity is regarded unlikely by medical history or has been ruled out by laboratory testing (Grade C).
3. Recommendation relating to 'pharmacodynamically relevant (i.e. active) drug concentrations' (Grade C).

a. For VKA: In acute stroke patients on VKA, INR should be measured. An INR $\leq$1.7 allows IVT in AIS. For ICH patients,

i. an INR >2 should trigger reversal treatment with prothrombin complex concentrate (PCC) 30 U/kg.

ii. an INR >1.2 should trigger reversal treatment with PCC 10 U/kg.

b. For NOACs: Relevant drug concentrations in patients on NOACs should be assumed if:

i. Global routine tests are above normal

1. Activated Partial Thromboplastin Time (aPTT) for dabigatran
2. Prothrombin time (PT) for rivaroxaban and edoxaban; however, PT should not guide therapy in cases involving apixaban

ii. Non-calibrated tests are above normal

1. Ecarin clotting time (ECT) for dabigatran
2. Factor Xa-activity tests for factor Xa-inhibitors

iii. Calibrated tests provide information as below:

1. If diluted thrombin time (dTT) for dabigatran indicates concentration >30 ng/ml
2. If factor Xa-activity tests calibrated for factor Xa-inhibitors indicate concentration >30 ng/ml

If calibrated tests are available, their thresholds may guide therapy

Issue 2A: Management of AIS and indication for reperfusion therapy during treatment with VKAs

1. In patients with AIS and indication for reperfusion therapy during therapy with VKA and an INR $\leq$1.7, thrombolysis should be performed (Grade C).
2. In patients with AIS during therapy with VKA and an INR >1.7, thrombolysis should not be performed (Grade C).
3. Patients with AIS during therapy with VKA who suffer from large vessel occlusion with indication for reperfusion therapy should be offered thrombectomy (Grade C).

Issue 2B: Management of acute ICH during treatment with VKAs

1. In adult patients with ICH related to VKA and with an INR $\geq$2, intravenous 4-factor-PCC in a dose of at least 30 U/kg should be administered to normalise the INR and limit haematoma expansion (Grade B). Reversal of anticoagulation with

PCC may also be initiated at INR between 1.2 and 2.0 with lower PCC-dose of 10 U/kg (Grade C).
2. Reversal with fresh frozen plasma is not recommended (Grade C).
3. Administration of vitamin K (10 mg, iv) may be considered if the initial INR $\geq$1.2 on repeated measurements (Grade C).

Issue 3A: Management of AIS and acute ICH occurring during treatment with non-vitamin K oral anticoagulants
1. In adult patients with AIS related to factor Xa-inhibitors and suspicion or evidence of relevant drug concentrations, IVT should not be performed (Grade C).
2. In adult patients with AIS related to dabigatran and the suspicion or evidence of relevant drug concentrations, IVT cannot presently be recommended (Grade C).
3. In adult patients with AIS related to NOACs, thrombectomy should be performed consistent with recommendations for non-anticoagulated patients (Grade C).

Issue 3B: Management of acute ICH occurring during treatment with NOAC
1. In patients with ICH related to dabigatran, idarucizumab 2×2.5 g should be injected (Grade B).
2. If idarucizumab is not available, PCC may be infused (30–50 U/kg) (Grade C).
3. In patients with ICH-related to apixaban, edoxaban or rivaroxaban PCC (30–50 U/kg) should be used (Grade C).
4. Reversal of NOAC with fresh frozen plasma is not recommended (Grade C).

Session 7: IV thrombolysis in AIS-dosing of alteplase

Chair: M. Dichgans (Munich), Session secretary: K. Kostulas (Stockholm), Speakers: T. Robinson (Leicester), W. Hacke (Heidelberg)

1. Do the results of the ENCHANTED study support a recommendation of a dose of 0.6 mg/kg of alteplase for iv thrombolysis for an Asian population?
   a. Standard-dose intravenous alteplase (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose given as a bolus followed by a 60-min infusion, is recommended within 4.5 h of onset of ischaemic stroke (Grade A).
   b. Ethnicity should not be used as a reason for not offering best treatment, i.e. standard-dose alteplase (Grade B).
2. Do the results of the ENCHANTED study support a recommendation of a dose of 0.6 mg/kg of alteplase for iv thrombolysis for a European population?

Where there is concern over symptomatic ICH risk, further RCTs are required to define the patient populations in whom low-dose intravenous alteplase (0.6 mg/kg body weight, maximum 60 mg) may be considered (Grade C).

Session 8: Management of symptomatic intracranial stenosis

Chair: D. Russell (Oslo), Secretary: M. Thorèn (Stockholm), Speakers: P. Ringleb (Heidelberg), M. Söderman (Stockholm)

1. Is intensive medical management the primary recommended therapy for the management of symptomatic intracranial stenosis?

Strict risk factor management and optimal medical therapy is the primary recommended treatment for the management of symptomatic intracranial stenosis (Grade B evidence).

2. If so, are there subgroups of patients for which angioplasty and/or stent placement would offer a better or equivalent alterative?

There is not enough evidence to recommend situations where angioplasty and/or stent placement would offer a better or equivalent alterative. Although there is no evidence, the role of angioplasty and stenting, carried out by experienced personnel, may be considered in a few special situations (Grade C evidence).

RCTs or prospective registry studies are therefore required.

Session 9: How to reach a cognitive endpoint in stroke trials?

Chair: V. Caso (Perugia), Secretary: I. Markaki (Stockholm), Speakers: M. Brainin (Krems), D. Leys (Lille)

Aims for this session:

1. Strategies that guarantee that cognitive endpoints are included in future major stroke studies/trials
2. Neuropsychological tests for best identifying cognitive endpoints
3. Appropriate tailor strategies for the education of clinicians and researchers on the interplay between stroke and dementia
   - Cognitive endpoints should be included in all stroke trials (Grade C).

- The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) or equivalent should be included in acute stroke trials to be sure that groups are balanced for pre-existing cognitive impairment.
- Two versions of neuropsychological test batteries may be considered within 3 to 6 months post stroke: a short version that can be conducted by trained nurses or physicians, and a more comprehensive long version that has to be performed mostly by trained neuropsychologists.

The short test battery could include the Montreal Cognitive Assessment (MoCA), the Trail Making Test A and B and the digit span forward and backward.

An extended test battery should assess multiple domains and be composed of validated neuropsychological tests fulfilling different criteria regarding psychometrics, usability, costs, time, language and culture.

- Sample sizes and duration of follow-up should be taken into account in prevention trials to evaluate cognitive outcomes.
- It is advisable to include also a short depression scale, a self-rating scale such as the Beck Depression inventory or the Centre of Epidemiologic Studies Depression scale.
- Focus on longstanding effects of interventions should also consider assessment of fatigue and apathy, as well as caregiver status.

Session 10: Prehospital triage for mechanical thrombectomy

Chair: U. Fischer (Bern), Secretary: M. Mazya (Stockholm), Speakers: D. Damgaard (Aarhus), A. Davalos (Barcelona), M. Mazya (Stockholm)

A. Clinical identification of stroke patients with large vessel occlusion: Current evidence and limitations

1. Several published clinical scores to predict large artery occlusion (LAO) appear to have similar predictive performance in the range of 70–80%, resulting in 20–30% of patients with LAO being missed at optimal score cut-off levels. At the same cut-off levels, 12–25% of triage positive patients would not have a LAO (Grade C).
2. Studies validating the predictive performance of currently available LAO prediction scores should be performed in pre-hospital settings in unselected patients with a suspicion of stroke following initial contact with emergency medical services (Grade C).

B. Mechanical thrombectomy: 'Drip and ship' or 'load and go'?

3. For patients with a suspected LAO based on current clinical tools on field, there is uncertainty about the equipoise between drip and ship (that prioritizes early IVT and other standard of care therapies) and mother-ship (that prioritizes early endovascular thrombectomy) models. Data based on randomized controlled trials are needed to determine the most beneficial model for each particular patient (eligible or not for iv-tPA) in different geographical regions and to establish isochrones where a particular model may be beneficial (Grade C).
4. In the absence of evidence, for patients considered eligible to IVT in the field, if estimated transfer time to the nearest primary stroke centre is considerably shorter than time to a comprehensive stroke centre (approximately more than 30–45 min), the drip and ship model should be considered (Grade C).
5. In the absence of evidence, in a scenario where a primary stroke centre and comprehensive stroke centre are equidistant (approximately not more than 30–45 min apart) or when contraindications to IVT are known in the field, patients with suspected LAO in the field, should be considered for transfer directly to a comprehensive stroke centre, bypassing any closer primary stroke centres (Grade C).
6. In case of primary admission to a primary stroke centre, evaluation and treatment for patients with a possible LAO must be expeditious, to ensure a rapid secondary transfer to a comprehensive stroke centre, avoiding any sources of delay such as complex neuroimaging studies (i.e. perfusion studies) or waiting for effect of IVT. First picture to puncture time should be less than 90 min (Grade A).

Ethics approval

Not applicable.

Provenance

The Recommendations from the ESO-Karolinska Stroke Update Conference were not externally peer reviewed, as they are consensus documents that have been previously peer reviewed by the writing committee for each session. The manuscript was approved for publication by Bo Norrving as Editor-in-Chief and Didier Leys as Vice Editor.

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